Docket No.: 0933-0284PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Seppo SARNA et al.

International Application No.: PCT/FI2005/050061

Application No.: 10/598,606 Art Unit: 1631

Filed: December 14, 2006 Examiner: Michael L. Borin

For: A METHOD FOR PREDICTING THE STATE OF THE GASTRIC MUCOSA

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Seppo Sarna of the Department of Public Health, University of Helsinki, Finland, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am professor of biometrics and I have worked in this field for 35 years).

I am familiar with the above referenced patent application and the area of science for determining the state of the gastric mucosa, and determining the proper diagnosis, treatment, and healing of a patient suffering from diseases associated with atrophic gastritis and Helicobacter pylori gastritis.

I have read and understand the subject matter of the Office Action of June 4, 2009.

1. Rejection under 35 U.S.C. § 103

The Examiner rejects claims 1-12 under 35 U.S.C. § 103 as unpatentable over Väänänen et al or Suovaniemi in view of García-Fernández et al.

2. Väänänen et al.

Väänänen et al. do not disclose the algorithm exploited in this invention for at least the following reasons. First, to effect the present invention, models based on multiple variables (multinominal regression) are needed. The decision algorithm of the present invention produces a deterministic decision, but also probabilities of the certainty of the decisions. This leads to a more precise diagnosis and enables prediction of multiple diseases from one patient sample. It is also important that the result is obtained as a numerical value (i.e. the probability value), as if it were quantitative, which enables monitoring of the change of the state of the patient (effect of the treatment / healing / development of the disease).

The present invention uses a "Path Model" developed by the present inventors (see also the scheme enclosed). It is based on gastric biomarkers analyzed from blood plasma. It is a computational multivariate model for diagnosis of *Helicobacter pylori* gastritis and atrophic gastritis.

3. The Path Model

a. Background

Many different computer programs for constructing multivariate reference values in clinical chemistry have been presented during last three decades. In general, however, the aim of these attempts has been the creation of multivariable reference limits ("normal ranges") for independent laboratory parameters in simultaneous analyses of huge number of samples, without trying to concentrate on diagnosis of specific diseases.

In medicine, getting a specific diagnosis of a disease is usually based on the simultaneous consideration of the results of more than one independent, or sometimes even contingent, laboratory tests. Examples of this include stomach diseases in which two different com-partments, gastric antrum and corpus, form an interacting functional entity with

regulatory feedback links. The function of gastric corpus mucosa (acid secretion) affects the function of gastric antrum (secretion and synthesis of gastrin-17 from antral G cells), and vice versa. Alteration in the structure or function of one of the compartments results in changes in functions of the other compartment. This will also result in changes in blood biomarkers of both compartments. Therefore, a comprehensive laboratory diagnosis of gastric diseases, or a diagnosis of a healthy stomach mucosa, requires consideration of the laboratory results specific for both antrum and corpus. Both compartments have different, specific plasma biomarkers, the changes of which should be taken into account when diagnosing the condition of the stomach mucosa.

Helicobacter pylori (*H. pylori*) infection is ultimately the most important pathogen in stomach diseases. *H. pylori* infection causes chronic gastritis that appears as an active mononuclear inflammation in both antrum and corpus. This inflammation will result in the destruction (atrophy, atrophic gastritis) of the structure and function of the mucosa in half of the infected persons during the course of decades. Practically all of the clinically important gastric diseases (peptic duodenal or gastric ulcers, gastric cancer, malabsorptions of some vitamins and micronutrients due to atrophic gastritis and hypochlorhydric stomach, etc.) result from the initial *H. pylori* gastritis, and of the subsequent atrophic gastritis either in antrum, corpus, or both.

b. Gastric biomarkers in blood plasma

H. pylori antibodies are the most reliable serological biomarker of an ongoing *H. pylori* infection. Plasma level of pepsinogen I (precursor of pepsin) and the ratio of plasma pepsinogen I to pepsinogen II are excellent biomarkers for the structure and function of the gastric corpus. They linearly decrease with increasing grade of atrophic gastritis in corpus, and in this way their levels reflect the ability of the stomach mucosa to secrete acid, and intrinsic factor. Gastrin-17 in secreted solely by G-cells in the gastric antrum, and its plasma level reflects the number of G-cells in the antral mucosa. The more severe is atrophic gastritis in the antrum, the lower is the number of G-cells, and thus the level of gastrin-17 in plasma. The level of gastrin-17 also reflects the level of acid secretion from the gastric corpus. These parameters (*H. pylori* antibodies, pepsinogens I and II, gastrin-17) constitute an established

functional entity and can be used in the non-invasive diagnosis of the state of gastric mucosa. This diagnosis is formed by simultaneous analysis of the four plasma biomarkers. For this purpose, a computational "Path Model" was developed, based on the available biomarker data combined with histological, endoscopical observations in large outpatient series, using a population-based sample of subjects as reference.

c. The "Path Model"

The Path Model focuses on making diagnoses of an ongoing Helicobacter pylori gastritis and/or atrophic gastritis. In addition, the model effectively screens out those persons who have a healthy gastric mucosa, who do not require gastroscopy, an invasive procedure. The Path Model also enables follow-up study of the state of the gastric mucosa of a patient when repeated serum samples are collected after initial diagnosis (and treatment).

The model is a combination of five multivariable sub models targeted to diagnose *Helicobacter pylori* infection and atrophic gastritis, using laboratory tests available as GastroPanel (Biohit Oyj, Helsinki, Finland). The serological markers used in the models are blood pepsinogen I (PGI), pepsinogen II (PGII), PGI/PGII, IgG and IgA combination test for Helicobacter pylori (HpAb), and basal and stimulated gastrin 17 (g17b and g17s). The path model gives both probabilities and deterministic decision rules for making choices between the following diagnoses: "Normal gastric mucosa" (Sub models 1,2,3) , "Helicobacter negative non-atrophic gastritis" (Sub models 1,2,3), "Helicobacter negative atrophic gastritis" (Sub models 1 and 2), "Helicobacter positive non-atrophic gastritis" (Models 1and 4), "atrophic gastritis in corpus" (Sub models 1, 4 and 5), "atrophic gastritis in antrum" (Sub models 1, 4 and 5) and "atrophic pangastritis" (Sub models 1, 4 and 5). In addition, the path model gives probabilities of *Helicobacter pylori* infection and atrophic gastritis without specifying the site of gastritis. If the site is demanded, the g17s result must be included to get data for sub model 5.

d. Reference population group (Kalixanda population sample)

Two adjacent communities in the northern part of Sweden, Kalix and Haparanda ("the Kalixanda" population), had 28,988 inhabitants in December 1998, with the distribution of age and gender similar to the national average in Sweden, although the socioeconomic level was only slightly lower. From all adults (n= 21, 610, 20-80 years of age), a random study population (n=3,000) was sampled with a procedure equivalent to random sampling. All eligible subjects (n=2, 860) were sent by post a validated postal questionnaire (the Abdominal Symptom Questionnaire, ASQ), with two reminder letters when needed and 2,122 (74.2%) replied. In random order, irrespective of age, sex and eventual symptoms, 1,001 subjects accepted undergoing an upper endoscopy, of which one refused biopsies. The response rate was 73.3% among those eligible. Serology assays were available in 998 of the 1,001 subjects. The endoscoped sample has been shown to be representative of the general population.

Consequently, the method of the invention specifically facilitates the follow-up study of the state of the gastric mucosa of a patient. Neither Ashton et al. (classification of imaging data) nor García-Fernández et al. (finding risk factors for death) have any reason for a follow-up study.

The Examiner is of the opinion that although Väänänen et al. and Suovaniemi et al. do not teach determining probability for the gastric mucosa to belong to atrophic gastritis tissue, it is known, e.g. from Ashton et al. that when a plurality of parameters are known, probability of a tissue to belong to a certain type can be determined using "probability maps". While it is true that Ashton et al. uses a statistical method (maximum likelihood estimation) similar to that used in the present invention, the algorithm of Ashton et al. (classification of MRI imaging data) and the Path Model algorithm of the present invention are quite different. The same is valid also for the García-Fernández et al. reference; the basis for the study is quite different.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: Oct. 29, 2009

Dr. Seppo Sarna

CURRICULUM VITAE

Seppo Sarna, Ph.D, 66, Professor of Biometrics at the Department of Public Health University of Helsinki Finland. Education: M.Sc. in 1966 in Mathematics, Ph.lic. in 1970 in Applied Mathematics, Ph.D. in 1977 in Statistics at the University of Helsinki. Continuing education(selected): Course in Cancer Epidemiology, IARC Lyon 1978, Summer School in Epidemiology at the University of Minneapolis in 1981 (Cardiovascular Diseases, Advanced methods of Statistics, Cancer and Genetics, 20 credits each), Summer School in Epidemiology (Infectious Diseases, AIDS)at the University of Johns Hopkins, Baltimore 1988. Employment: in 1967 - 1971 Mathematician, Computer Centre, University of Helsinki, 1971 Acting Professor of Computer Science, University of Oulu, in 1972 - 1973 Acting Associate Professor of Numerical Analyses, in 1974 - 1978 Acting Associate Professor of Biometrics, in 1978- Associate Professor of Biometrics, 1984 - 1989 Acting Professor of Public Health, University of Helsinki. Number of original publications 340, number of other publications 20 and number of congress abstracts 150.